· WO 99/58968

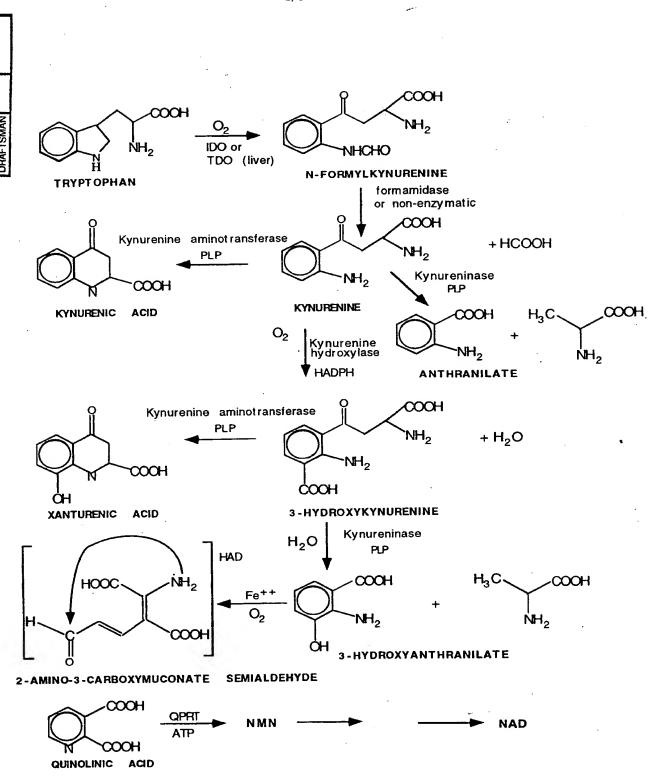


Fig.1. Kynurenine pathway and related enzymes. Abbreviations: IDO, indoleamine 2,3-dioxygenase; TDO,tryptophan 2,3-dioxygenase; PLP, pyridoxal 5' phosphate; HAD, 3-hydroxyanthranilate 3,4-dioxygenase; QPRT, quinolinate phosphoribosyltransferase

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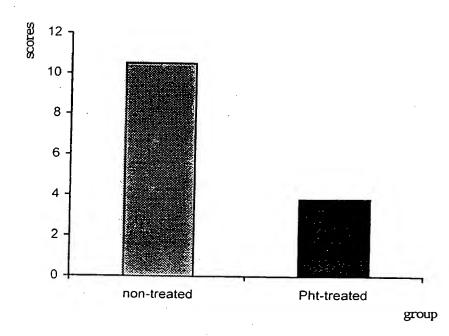
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APPROVED O G. FIG. Table 1 DRAFTSMAN λ Plasma kynurenines in epilepsy-prone (EP) rats and rats with spontaneous non-convulsive

Effect of anticonvulsive drugs (phenytoin and ethosuximide) on plasma kynurenines absence seizures (GAERs) in comparison with control epilepsy-resistant (ER) rats

	TRP	KYN	3HOKYN	3HOAA	₩	\$	KA/3HOAA	KA/3HOAA (AA+KA)/3HOAA
ER	43.5±1.4	3.4±1.5		10.7±6.5	188.6±37.1	188.6±37.1 260.0±227.5 37.9±33.5	37.9±33.5	55.4±29.2
ËP	59.0±7.6	0.5±0.2		18.5±2.3	18.5±2.3 411.4±122.4 21.1±9.6	21.1±9.6	1.1±0.5	23.3±6.5
EP/Pht chronic.	38.8±14.0	3.1±0.8		13.4±3.4	446.3±31.2	446.3±31.2 370.5±253.6 45.8±39.3	45.8±39.3	74.2±56.6
GAERs	54.8±9.4	0.9±0.4		13.2±4.1	111.6±60.2	42.5±30.0	3.6±2.7	13.0±10.8
GAERs/Ets		6.1±2.7	0.8±0.2	21.6±3.5	21.6±3.5 930.0±150.5 672.0±208.0 37.9±12.9	672.0±208.0	37.9±12.9	85.8±31.9
GAERs/Ets chronic.	28.1±2.2	0.37±0.03		23.6±6.5	142.7±54.6	36.6±22.2	1.4±0.5	8.4±3.1

FIG. 2

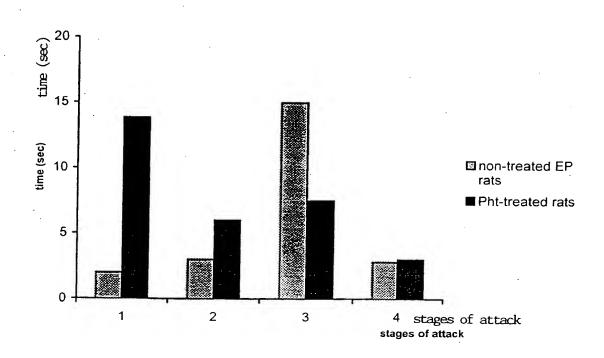


Scores:

- 0 -- absence of reactions
- 1 -- short-term wild running
- 2 --two phase wild running
- 4 --tonic convulsions of flexors
- 6 --tonic convulsions of extensors
- 8 --postictal excitation or muscular atonia
- 10 -postictal excitation with convulsions
- 12 -postictal coma
- 16 -lethal exit

FIG. 3A





Stages of attack:

- 1. Latency
- 2. Wild running
- 3. Tonic convulsions of flexor or/and extensors
- 4. Clonic convulsions

Postictal condition	Non-treated	Pht
immobility	0/9	11/11
excitation	3/9	0/11
coma	6/9	0/11

FIG. 3B

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APPROVED O G. FIG. Brain kynurenines in epilepsy-prone (EP) rats in comparison with control epilepsy-resistant (ER) rats (per 1g tissue) DRAFTSMAN The second of the second secon

	The effect of phenytoin	toin						
	detabolites	TRP	KYN	3HOKYN	3HOAA	Ą	\$	3HOAA/TRP
TRP KYN 3HOKYN 3HOAA AA KA		mkM	mkM	mkM	Mu	Mu	Mc	
TRP KYN 3HOKYN 3HOAA AA KA KA MW MKM MKM MKM MKM MKM MKM MKM MKM MKM	a.	49.0±3.2	(3/6)	< 0.01	374 7+35 0	3 67 73 606	77777	11.00
TRP KYN 3HOKYN 3HOAA AA KA mkM mkM nM nM nM nM 49.0±3.2 (3/6) < 0.01 374.7±35.0 203.5±43.5 203.1±32.0	10/02+				0.00-1-1-10	404.0I43.0	707. II 124. I	1.7 ± 0.6
TRP KYN 3HOKYN 3HOAA AA KA mkM mkM nM nM nM nM 49.0±3.2 (3/6) < 0.01 374.7±35.9 202.6±43.6 282.1±124.1		5/.6±5.4		× 0.01	417.2±82.6	3(6)	1(6)	7 341 8
TRP KYN 3HOKYN 3HOAA AA KA mkM mkM nM nM nM nM 49.0±3.2 (3/6) < 0.01 374.7±35.9 202.6±43.6 282.1±124.1 57.6±5.4 < 0.01 417.2±82.6 3(6) 1/6)	8	42.5±7.6	1.63±1.2	< 0.01	2712+403	< 10	(4/5)	0.11.0

HIGOLOGIA							
Metabolites	TRP	KYN	3HOKYN	ЗНОАА	¥	Ϋ́	3HOAA/TRD
	mkM	mkM	mkM	Mu	Ma	Ma	
i.	0 00 000				IAII	IAIL	_
ניר	100.2±19.8	(2/2)	(1/5)	380.0+49.0	180 7+165 5	1151	20+02
				0:01=0:00	100.1 = 100.0	t.0	0.0 H O.0
EP/PN(145.3±44.1	(1/3)	× 0.01	464.0±184.8	< 10	(3/6)	2 240 4
£					2:-	(5/0)	0.4±0.4
בא	80.4±21.0	(1/6)	(5/6)	368.3±74.6	× 10	< 10	16101
						· ·	ナントラナ

Metabolites	TRP	Κ Κ Κ	3HOKYN	3HOAA	Ą	ΚA	3HOAA/TPD
	100	1.8					9110001111
	LIKIN	INKINI	E E	<u></u>	2	No.	
٥	0 74 . 4 70	30.0				IAII.	
	04.1±13.8	0.39		221 6+25 5	69 7+11 G	(3/6)	27+03
				2122	0.11-	000	C.U H U.S
r/rnt	97.2±19.1	3.48	× 0.01	288 3+120 g	50 1+A2 7	2 707	10.40
				-00:02 120:0	00.1-74.7	404.0	7.77
צ	104.0±11.4	0.56±0.23	(5/6)	288 0+52 0	< 10	(4/6)	0 0
				0.30000	0.1	9	4.0 ± 0.7

cerebellulii							
Metabolites	TRP	KYN	3HOKYN	3HOAA	Ą	Α¥	3HOAA/TRP
	mkM	mkM	mkM	Ma	Mac		100000
CL				INII	IAIL	IMU.	
ח	40.8±8.3	0.38 ± 0.3	0.07±0.055	36.4±18.0	(2/5)	81 1452 2	V 0 + 0 0
170/02	27.0.12				(513)	2.70-1.10	0.0 H 0.4
ברורוו	47.5±10.3	0.83	× 0.01	159.5±70.6	(2/4)	(1/1)	3 270 0
5					1 (12)	(+/)	0.0HO.0
בא	41.6±1.2	0.16	(5/6)	98.9±28.1	v 10	< 10	30176
					•	> -	7.4 H O.O

*/ in brackets the numbers of individual measurements out of the number of analysed samples are indicated

brain stem

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APPROVED O 3. FIG. DRAFTSMAN

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GAERs)	
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in comparison with epilepsy-resistant (ER) rats (per 1g tissue).

Effect of ethosuximide

cortex Metabo GAER GAER GAER

Table 3

abolites	TRP	X X	3HOKYN	3HOAA	A A	₹	SHOAWIRE
	mkM	mkM	mkM	Mu	Mn	Mn	
	42.5±7.6	1.63±1.2	< 0.01	271.2±40.3	< 1.0	(1/5)	6.6± 1.3
-Rs	66.45 ±3.4	<0.01	<0.01	464.75 ± 85.2	< 1.0	(117)	7.0 ± 1.3
Rs Ets	40.8 ± 6.9	(1/10)	<0.01	250.6 ± 62.8	(4/10)	(1/10)	6.1±1.0
Rs Ets chronic.	60.5 ± 5.8	(2/6)	<0.01	572.8 ± 62.8	< 1.0	< 1.0	9.5 ± 1.7

	1 222	14/4/1	NAMOUS	VVODE	VV	VΧ	1 2HOAA/TRP
Metabolites	אר ד	NTN	NINOLIS	A COLOR	ξ	5	2010
	mkM	mkM	mkM	ШM	Mu	Mu	
ER	80.4±21.0	(1/6)	(2/6)	368.3±74.6	< 1.0	< 1.0	4.6±0.4
GAERS	78.6 ± 20.9	< 0.01	< 0.01	272.4 ±55.8	< 1.0	< 1.0	3.5 ± 0.5
GAERS ETS	51.0 ± 26.2	(2/10)	< 0.01	280 ± 69.1	235.9 ± 45.4	(2/10)	7.3±4.3
GAERs Ets chronic.	92.4 ± 23.7	(2/6)	< 0.01	235.3 ± 68.0	< 1.0	< 1.0	2.7 ± 0.8

brain stem

Metabolites	TRP	KYN	3HOKYN	3HOAA	AA	ΚΆ	3HOAA/TRP
	mkM	mkM	mkM	Mn	иМ	Mn	
ER	104.0±11.4	0.56±0.23	(2/6)	288.0±52.0	< 1.0	(1/6)	28 ± 0.4
GAERS	116.2 ± 16.5	0.33 ± 0.18	< 0.01	315.3 ± 127.8	< 1.0	(4/1)	2.6 ± 0.7
GAERS Ets	49.9 ± 7.9	0.18 ± 0.15	< 0.01	200.3 ± 42.7	(1/10)	(4/10)	4.1 ± 0.8
GAERs Ets chronic.	76.7 ± 23.7	0.43 ± 0.38	< 0.01	196.7 ± 45.5	< 1.0	< 1.0	2.6 ± 0.3

cerebellum

Metabolites	TRP	Κ Κ Υ	3HOKYN	3HOAA	AA	¥.	3HOAA/TRP
	mkM	mkM	mkM	Mn	Mu	Μu	
E	41.6±1.2	0.16	(2/6)	98.9±28.1	< 1.0	< 1.0	2.4 ± 0.6
GAFRS	40.8 ± 5.73	(1/7)	(3/7)	70.5 ± 18.2	< 1.00	(2/7)	1.7 ± 0.4
GAERS Ets	26.4 ± 2.4	(1/10)	< 0.01	56.4 ± 54.9	(1/10)	(2/10)	2.1 ± 1.8
GAERs Ets chronic.	41.3 ± 3.5	0.26 ± 0.09	(1/6)	122.7 ± 65.1	< 1.0	< 1.0	4.2 ± 1.7

*/ in brackets the numbers of individual measurement out of the number of analysed samples are indicated

APPHOVED O G. FIG.

Plasma kynurenines in seizures-free epileptic patients and patients non-controlled by Antiepileptic drugs, in comparison with healthy children

										Table 4
	TRP KYN 3HOAA A	KYN	ЗНОАА	\$	₹	AA+KA	KA/3HOAA	(AA+KA)/3HOAA	KA/3HOAA/TRP	AA+KA KAJ3HOAA (AA+KA)/3HOAA KAJ3HOAA/TRP
Seizure-free	25.7±3.1	1.0±0.2	25.7±3.1 1.0±0.2 7.0±3.3 5.	5.1±1.5	34.8±5.8	39.8±7.9	1±1.5 34.8±5.8 39.8±7.9 5.0±1.5 5.7±2.6	5.7±2.6	0.16±0.04	0.22±0.08
Non-controlled	20.8±3.5	0.8±0.2	20.8±3.5 0.8±0.2 3.8±1.1 7.1	7.1±3.9	24.2±4.9	27.8±9.1	143.9 24.2±4.9 27.8±9.1 6.3±2.2 8.1±3.0	8.1±3.0	0.30±0.07	0.40±0.12
Healthy	29.8±4.9	1.3±0.3	29.8±4.9 1.3±0.3 8.6±4.8 4.	4.4±2.8	21.9±8.5	23.4±9.8	4±2.8 21.9±8.5 23.4±9.8 2.6±1.6 3.1±2.6	3.1±2.6	0.09±0.02	0.1±0.06

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FIG. 6

SUBSTITUTE SHEET (RULE 26)

900 wo 99/58968 11 10 4 10 05 11 20

APPROVED O 3: FIG.

BY CLUSS CUBCLASS
DRAFTSMAN

Plasma kynurenines in patients with repeated febrile convulsions in comparison with healthy children and children after the first episode of febrile convulsions

Table 5

	TRP	KYN	3HOAA AA		<u>₹</u>	AA+KA	KA/3HOAA	/ V V C I C I C I C I C I C I C I C I C I	- 00 1 6 4 7 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	AA+KA KA/3HOAA (AAA+KA)/AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA	
							10000		או אייט הנאיי	(NA+AA)/3HUAA/IRP	
Healthy	29.8±4.9	1.3±0.3	8.6±4.8	4.4±2.8	21.9±8.5	29.8±4.9 1.3±0.3 8.6±4.8 4.4±2.8 21.9±8.5 23.4±9.8 2.6±1.6		3.1±2.6	0.09+0.02	0 10+0 06	
Repeated febrile							l				8/8
convulsions	28.0±1.8	1.2±0.5	28.0±1.8 1.2±0.5 14.6±6.3 7.1±3.	7.1±3.2	22.3±8.9	2 22.3±8.9 29.4±10.7 1.5±0.5		2.0±0.4	0.05+0.01	0.07+0.0	
Febrile convulsions										70.04	
with family history	33.4±7.9	30±1.8	33.4±7.9 30±1.8 11.3±6.3 4.5±2.	4.5±2.0	25.0±9.6	.0 25.0±9.6 29.6±11.4 3.2±1.6		3.9+3.1	0.12+0.04	0 11+0 07	
Febrile convulsions										0.04	
without history	28.4±7.9	2.3±0.8	11.4±8.9	13.2±5.8	29.0±11.2	28.4±7.9 2.3±0.8 11.4±8.9 13.2±5.8 29.0±11.2 42.2±17.9 2.8±1.3		5.7±3.1	0.13±0.07	0.20±0.10	

FIG. 7